Mutation Research 762 (2014) 123–132

Contents lists available at ScienceDirect

Mutation Research/Reviews in Mutation Research

journal homepage: www.elsevier.com/locate/reviewsmr
Community address: www.elsevier.com/locate/mutres

Review

Anaplastic large cell lymphoma (ALCL) and breast implants: Breaking down the evidence

Xuan Ye [a,1,*], Kayvan Shokrollahi [b,1], Warren M. Rozen [c], Rachel Conyers [c], Penny Wright [d], Lukas Kenner [e,f,i,j], Suzanne D. Turner [g,i,1,**], Iain S. Whitaker [h,1,*]

[a] Prince of Wales Hospital, Randwick, New South Wales, Australia
[b] Mersey Regional Burns and Plastic Surgery Unit, Whiston Hospital, Liverpool L35 5DR, United Kingdom
[c] Peter MacCallum Cancer Institute, Melbourne, Victoria, Australia
[d] Department of Histopathology, Addenbrooke's Hospital, Cambridge, United Kingdom
[e] Ludwig Boltzmann Institute for Cancer Research, Wahringerstrasse 13A, Vienna, Austria
[f] Department of Laboratory Animal Pathology, University of Veterinary Medicine Vienna, 1210 Vienna, Austria
[g] Division of Molecular Histopathology, Department of Pathology, University of Cambridge, Lab Block Level 3, Box 231, Addenbrooke's Hospital, Cambridge CB20QQ, United Kingdom
[h] Institute of Life Science, Swansea University College of Medicine, Singleton Park, SA2 8PP Swansea, Wales, United Kingdom
[i] European Research Initiative for ALK-related Malignancies (ERIA)[2]
[j] Clinical Institute of Pathology, Medical University of Vienna, 1090 Vienna, Austria

ARTICLE INFO

Article history:
Received 1 July 2014
Received in revised form 12 August 2014
Accepted 13 August 2014
Available online 23 August 2014

Keywords:
Anaplastic large cell lymphoma
Breast implants
Bioprostheses
Anaplastic lymphoma kinase

ABSTRACT

Systemic anaplastic large cell lymphoma (ALCL) is a distinct disease classification provisionally sub-divided into ALCL, Anaplastic Lymphoma Kinase (ALK)$^+$ and ALCL, ALK$^-$ entities. More recently, another category of ALCL has been increasingly reported in the literature and is associated with the presence of breast implants. A comprehensive review of the 71 reported cases of breast implant associated ALCL (iALCL) is presented indicating the apparent risk factors and main characteristics of this rare cancer. The average patient is 50 years of age and most cases present in the capsule surrounding the implant as part of the periprosthetic fluid or the capsule itself on average at 10 years post-surgery suggesting that iALCL is a late complication. The absolute risk is low ranging from 1:500,000 to 1:3,000,000 patients with breast implants per year. The majority of cases are ALK-negative, yet are associated with silicone-coated implants suggestive of the mechanism of tumorigenesis which is discussed in relation to chronic inflammation, immunogenicity of the implants and sub-clinical infection. In particular, capsulotomy alone seems to be sufficient for the treatment of many cases suggesting the implants provide the biological stimulus whereas others require further treatment including chemo- and radiotherapy although reported cases remain too low to recommend a therapeutic approach. However, CD30-based therapeutics might be a future option.

Contents

* Corresponding author.
** Corresponding author at: Division of Molecular Histopathology, Department of Pathology, University of Cambridge, Lab Block Level 3, Box 231, Addenbrooke's Hospital, Cambridge CB20QQ, United Kingdom. Tel.: +44 01223 763655; fax: +44 01223 586670.
E-mail addresses: xuan.ye.888@gmail.com (X. Ye), sdt36@cam.ac.uk (S.D. Turner).
[1] These authors contributed equally to this work.
[2] www.ERIALCL.net.

http://dx.doi.org/10.1016/j.mrrev.2014.08.002
1383-5742/

1. Introduction

The first breast implant procedures were performed in the 1960s and, since then, between 5 and 10 million procedures have been performed worldwide [1,2]. In 2012, 286,000 breast augmentation procedures and 72,012 breast reconstructions were performed using implants in the United States alone [2]. Whilst breast implant surgery can confer 'life-enhancing' benefits for women, it remains unclear whether the breast implants are carcinogenic.

In the last two decades, a number of case reports have documented the occurrence of anaplastic large cell lymphoma (ALCL), a rare type of non-Hodgkin lymphoma (NHL), in the capsule surrounding breast implants. This has led to the hypothesis that ALCL may be a late complication of the procedure and reviews of between 27 and 34 case reports have been conducted by various medical and governmental institutions in an attempt to ascertain the exact relationship between ALCL and breast implants [3–29]. However, very few publications have sought to examine the possible mechanisms or evaluate the evidence underpinning this topic.

In this review we present an updated summary of the published cases of iALCL (71 cases) and discuss potential mechanisms towards the pathogenesis of this disease.

1.1. ALCL

Systemic ALCL is a T-cell lymphoma predominantly affecting the paediatric and young adult patient population when anaplastic lymphoma kinase (ALK) positive and adults (40–65 years) when ALK− with a male predominance in both cases (male:female ratio of 1.5:1) [30,31]. It can present at both nodal and extranodal sites, the latter including skin, lung, liver, soft tissue and bone [31–34]. Histopathologically, it is a heterogeneous disease with a number of morphological variant forms including small cell, lymphohistiocytic, Hodgkin-like and common forms [35]. ALCL is further sub-divided into two provisional entities, ALK positive and negative, the former being more common [35].

1.1.1. ALCL, ALK+

ALCL, ALK+ has a relatively good prognosis with a 5 year overall survival of 80% (70% when paediatric patients are excluded) and whilst the rate of relapse is high (30%), most patients remain sensitive to chemotherapy [36]. ALK is expressed in ALCL as the consequence of a chromosomal translocation whereby the ALK gene on chromosome 2 becomes juxtaposed to a variety of partner genes, but most commonly *Nucleophosmin* (NPM) on chromosome 5 [37]. The fusion gene retains the oligomerisation domains of NPM together with the kinase domain of ALK resulting in the production of a constitutively active intracellular tyrosine kinase activating a plethora of signal transduction pathways key amongst which is STAT3 [38,39]. Hyperactive ALK-induced signalling is key to cellular transformation and small molecule inhibitors of this protein hold much promise in the future treatment of this disease [40].

1.1.2. ALCL, ALK−

In contrast to ALCL ALK+, ALCL ALK− cases have a poor prognosis with an overall survival at 5 years of 49% [31]. Unlike for ALCL, ALK+, the driving oncogenic events in ALCL, ALK− are unknown as there are no detectable recurrent cytogenetic events although recently a translocation, t(6;7)(p25.3;q32.3) resulting in down-regulation of DUSP22 has been detected in 18% of ALCL, ALK− [41]. In addition events inactivating/inducing expression of genes including PRDM1/BLIMP1, TNFRSF8, BATF3, and TMOD1 as well as miRNA have been reported [41–44]. However, their relative importance towards the pathogenesis of ALCL, ALK− remains to be determined.

1.1.3. Cutaneous ALCL

Cutaneous ALCL (C-ALCL; as opposed to systemic ALCL with cutaneous involvement) belongs to the diagnostic category of primary cutaneous CD30-positive T-cell lymphoproliferative disorders [35]. Like ALCL, ALK− it mostly affects adults with a median age of 60 and is also ALK− with patients having a favourable prognosis with a 10 year survival rate of 90% [45,46].

1.1.4. ALCL of the breast (non-implant associated)

If ALCL, ALK− is rare, then ALCL presenting in the breast is almost non-existent. Of the 27 worldwide reported cases of non-implant associated ALCL, one third are ALK− and two thirds are ALK+ [15]. The mean age of the patients at disease presentation is 50 for the ALK− and 37 years for the ALK+ cases and the disease presents as a diffuse spread throughout the breast tissue [15]. Due its extreme rarity, prognosis of ALCL of the breast is unknown.

1.1.5. ALCL associated with breast implants

Implant-related ALCL (iALCL) occur in close proximity to the implant capsule, either as part of the periprosthetic fluid or in the capsule itself [6,15,47–49]. From our review, the typical patient with iALCL is ~50 years old, previously healthy (although half of patients had reconstructive surgery following breast cancer) and received a silicone-coated implant a decade before for cosmetic purposes (Table 1). The most common presenting complaint was late seroma 10 years following implantation (range: 1–32 years) [22,50–52]. This was followed by the presence of a palpable mass

Table 1
Summary of patient and implant characteristics.*

Number of cases	71
Patient characteristics	
Age	
Range	28–87
Mean	51.49
Previous breast cancer	
Yes	28
No	29
Not reported	14
Previous lymphoma	
Yes	5
No	52
Not reported	14
Implant characteristics	
Coating material	
Silicone	45
Polyurethane	2
Not reported	24
Filling	
Silicone	24
Saline	30
Not reported	17
Implant leak	7
Indication	
Cosmetic	25
Reconstructive	13
Not reported	29
Years between implant and ALCL	
Range	1–32
Mean	9.97

* Note that five patients had a previous history of lymphoma. Of these, information on the subtype of disease was only provided for 3 cases: 1. Hodgkin's Lymphoma; 2. ALK$^+$ cutaneous ALCL; 3. ALK$^-$ cutaneous ALCL.

Table 2
Summary of clinical presentation and treatments used.

Presentation	
Seroma	37
Mass	22
Contracture	10
Pain	11
Inflammation	7
Swelling	13
B Symptoms	2
Lymphadenopathy	2
Treatment	
Surgery	
Implant removal	51
Capsulotomy	36
No surgery	4
Not reported	14
Chemotherapy	
CHOP	26
ICE	3
ESHAP	2
GIV	2
Not reported	28
No chemotherapy	12
Radiotherapy	
Yes	30
No	28
Not reported	13
Follow-up (weeks)	
Range	1–52
Mean	15
Resolved	41
Recurrence/relapse	3
Deceased	5
Not reported	22

or notable capsular contraction (Baker grades III and IV; a measure of the extent of capsular contraction ranging from I to IV, I being relatively normal to IV, the breast being hard, painful to the touch and abnormal in appearance). Very few complained of systemic symptoms (Table 2). Diagnosis was most commonly established with the triple assessment (clinical evaluation, imaging and cytology). Fig. 1 shows a typical histopathological presentation of iALCL whereby hallmark lymphoma cells are apparent as is positive cell surface and cytoplasmic staining for CD30. Most women had early stage disease which responded favourably to surgery, chemotherapy and radiation possibly due to the removal of carcinogenic stimuli with implant removal and capsulotomy (Table 2) [15,22,23,47–49,53,54]. However, an unfortunate few have been reported to relapse and die following disease progression (Table 2).

Typically iALCL is ALK- as shown in Fig. 1d although one case has been reported as ALK$^+$ [21]. Interestingly, in the example presented in Fig. 1, weak staining for ALK is apparent and this correlates with an increase in ALK gene dosage to 5 copies as assessed by FISH using an ALK break apart probe; ALK amplification has been implicated in other cancers, most notably neuroblastoma and therefore the relevance of ALK to iALCL remains to be fully elucidated.

2. Is breast implant-associated ALCL a distinct disease entity?

2.1. Comparison of iALCL with systemic ALCL, ALK$^+$ and ALK$^-$

Histopathologically, iALCL presents similarly to systemic ALCL regardless of ALK status although given the predominance of ALK- cases it likely better aligns with ALCL, ALK$^-$ especially given the older diagnostic age. However, survival rates are higher as is the case for ALCL, ALK$^+$ and therefore iALCL is probably best described as another provisional entity of ALCL hence giving rise to four categories, iALCL, C-ALCL, ALCL ALK$^+$ and ALCL ALK$^-$.

2.2. Comparison of NHL of the breast between patients with and without breast implants

NHLs in patients without breast implants are a histologically heterogeneous group of lymphomas mostly accounted for by diffuse large B-cell and follicular sub-types; T-cell lymphomas are rare [11,27]. In contrast, NHLs in breast implant patients are histopathologically uniform (i.e. >80% are ALCL) and outnumber their non-ALCL counterparts by approximately 5–1 [6,15,47–49]. However, ALCL has also been reported in the breast in the context of patients that do not have breast implants but there are still significant differences in disease presentation in both scenarios. For example, the majority of iALCL are ALK$^-$ (61/62 reported) whereas two thirds of those not associated with breast implants are ALK$^+$ suggestive of differing mechanism of tumorigenesis [6,15,47–49].

In addition, all breast iALCL occur in close proximity to the implant capsule whereas those in patients without implants are diffuse [15]. Lastly, whilst the diagnosis of ALCL of the breast is of a low incidence, most of these cases have been reported in association with breast implants (42/69). These data support the proposition that NHLs of the breast are distinct depending on the patient class in which they appear.

2.3. Incidence of ALCL in breast implants versus other bioprostheses

Notwithstanding the above biological distinctions between iALCL and those occurring in the absence of breast implants, there are counterarguments to the proposition that there is a specific association between breast implants and a certain subtype of ALCL,

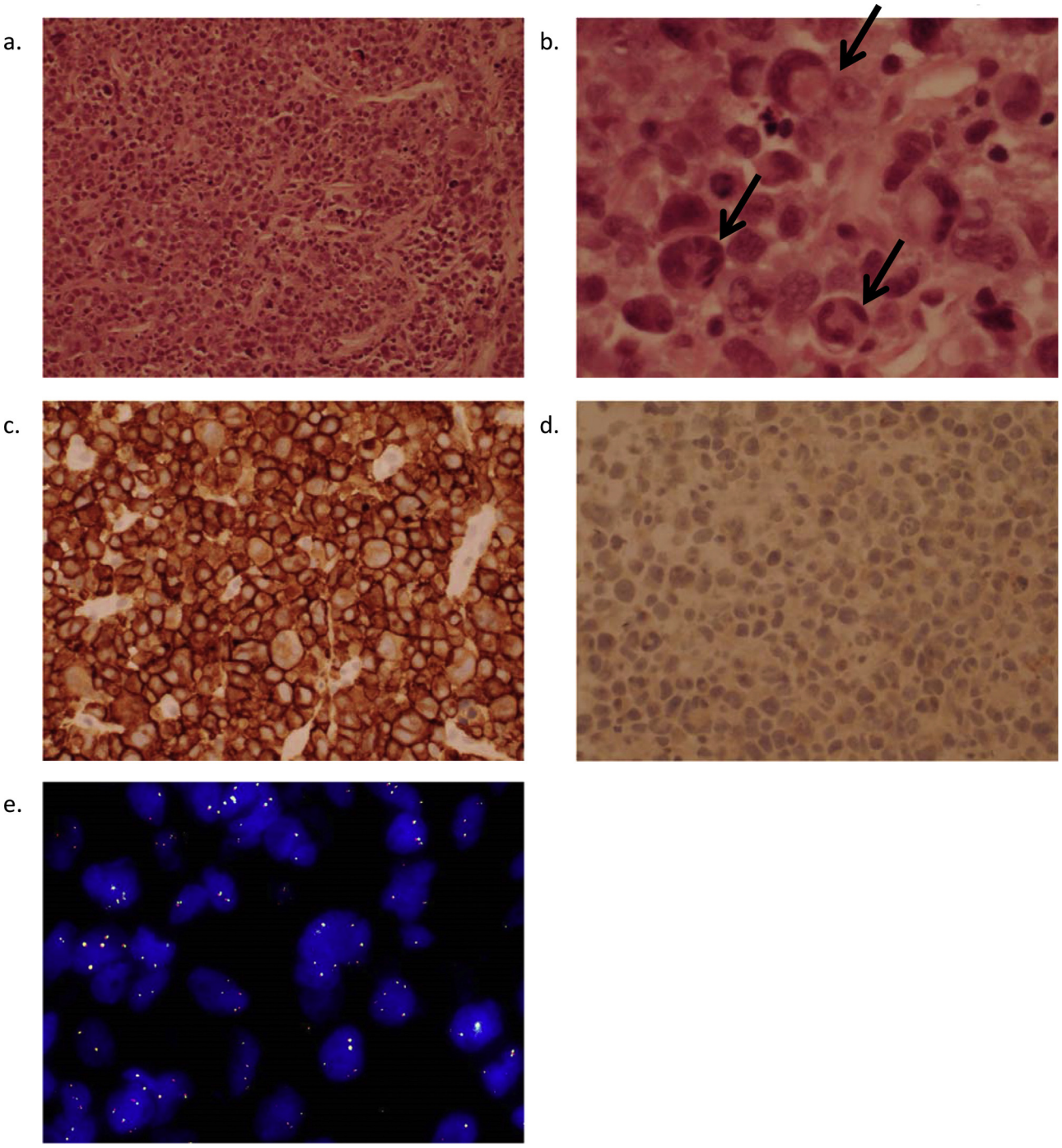

Fig. 1. Histopathological presentation of breast implant-associated ALCL showing large hallmark cells with pleomorphic nuclei and abundant cytoplasm. (a) A 20× H&E image. (b) A 100× H&E image taken under oil immersion showing hallmark cells (indicated by arrows). (c) Immunohistochemistry for cell surface CD30 expression, 40×. (d) ALK staining 40×. (e) Interphase FISH using an ALK dual-colour break-apart probe (Vysis LSI®) showing five copies in most nuclei.

to the effect that the disproportionate frequency of ALCL that has been observed in breast implant patients as compared to the general population may simply be attributable to a higher overall incidence of lymphomas and cancer in patients with prostheses in general.

The occurrence of periprosthetic NHL (mostly B-cell lymphoma) has been reported in the setting of orthopaedic and cardiac prostheses [55–61]. Epidemiological studies comparing cancer rates between patients with joint replacements and the general population have found similar rates of NHL in patients with hip and knee prostheses to that observed in patients with breast implants (SIR = 0.98–1.16 and 1.20–2.19, respectively) [58,59,62]. However, these studies included 95% confidence intervals of 1.0, so the association between orthopaedic devices and cancer risk is still unclear. The preliminary conclusions from these orthopaedic studies appear to be closely aligned with the findings in breast implant literature that there may be a small but statistically insignificant risk of NHL in patients with prosthetic devices.

This evidence examined alone seems to suggest that the development of lymphomas around prosthetic devices may be a generalized pathological phenomenon arising from the prolonged presence of foreign materials, rather than a phenomenon that is unique to breast implants per se. However, although NHLs (mostly B-cell lymphomas), sarcomas and other soft tissue tumours have

been noted to occur in close proximity to prosthetic devices, there has only ever been *one* reported case of ALCL in a non-breast prosthesis (a stainless steel plate) [59]. These facts support the idea that iALCLs occur virtually exclusively in the context of breast implants.

2.4. Cancer rates in breast implant patients versus the general population

Existing literature suggests that NHLs in general account for between 0.04 and 0.5% of all breast malignancies [27]. In contrast, a case–control study conducted by de Jong et al. [6] estimated the incidence of ALCL in the breast to be between 0.0001% and 0.0003% of all women with breast prostheses per year. These results represent a relative risk of 18.2 that ALCL will occur in women with breast implants compared to those without breast implants, although it is noted that the absolute risk is still extremely low at between 1:500,000 and 1:3,000,000 patients per year according to existing studies [6,29]. These figures are yet to be confirmed with further studies and, with an increasing global awareness of this disease, it is possible that the reported incidence of iALCL may change in light of updated numbers of case reports and will need to be re-evaluated when the corresponding registry data becomes available.

Despite these findings, a counterargument to the association of breast implants and ALCL is that the breast implant population experiences a higher overall incidence of cancer than the general population, such that the elevated incidence of ALCL in women with breast implants is no more than a 'chance' observation. According to the results of our review, this does not appear to be the case.

We identified six epidemiological papers that compared the risk of cancer between patients with breast implants and the general population [63–70]. In 2001, Brinton et al. [63] retrospectively analyzed the incidence of cancer in 13,488 patients with breast implants and found that malignancies of the cervix (SIR = 3.18), vulva (SIR = 2.51), stomach (SIR = 2.65) and brain (SIR = 2.16), as well as leukaemia (SIR = 2.19), occurred with greater frequency in breast implant patients than in the general population. However, the paper conceded that the increased relative risk of these cancers was most likely attributable to lifestyle differences between the two populations rather than the presence of breast implants.

One year later, a Finnish study compared the rate and stage of cancer in 2171 breast implant patients recruited from private plastic surgeries against the Finnish national registry. The study found no evidence that cancers in the implant population occurred at a higher rate or were at a more advanced stage than in the general population (SIR = 0.90), with the exception of non-melanoma skin cancer (SIR = 1.1) which was again attributed to possible lifestyle factors between the two patient populations [68]. These results were echoed in four other studies by Friis et al. (SIR = 0.70), Deapen et al. (SIR = 0.69), McLaughlin (SIR = 1.0) and Lipworth et al. (SIR = 0.95) [64–66,70].

Ultimately, none of the six studies found any increase in the incidence of breast cancer or lymphoma compared to the general population. In fact, the majority of these studies (i.e. SIR < 1.0) seem to suggest that cancer rates are *lower* in breast implant patients than the general population. Accordingly, based on the available evidence, it does not seem that the disproportionate frequency with which ALCL has been observed in breast implant patients is the result of higher cancer rates in the breast implant population.

Furthermore, overall cancer rates have also been extensively examined in the setting of other bioprostheses, such as joint replacements, through data collected in national registries [60,71–74]. Although the conclusions of these reports are still the subject of debate, it appears that patients with hip and knee prosthesis may have an elevated risk of malignancy compared to the general population [60,71]. This in turn implies that breast implants may in fact have lower rates of malignancy compared with orthopaedic prostheses although the age group and selection biases between the two populations preclude a direct comparison of relative cancer risk.

3. What is (are) the mechanism(s) driving tumorigenesis for breast implant associated ALCL?

3.1. Chronic inflammation and the inflammatory milieu

Inflammation has been heralded as the seventh hallmark of cancer [75]. Epidemiological evidence suggests that chronic inflammatory states exhibit higher incidences of cancer [75,76]. Relevant examples include the association of T-cell lymphomas with coeliac disease, primary thyroid lymphoma with Hashimoto's thyroiditis, and marginal zone B-cell lymphomas with hepatitis C to list just a few. Conversely, non-steroidal anti-inflammatory medications are associated with a lower incidence of some cancers [75]. Although the precise mechanisms by which inflammation facilitates tumorigenesis remains unclear, it has been suggested that the dysregulated stromal microenvironment present in unresolved inflammation induces genetic instability through DNA injury and microsatellite instability, activates maladaptive homeostatic responses and dormant transcription factors, and subverts the immune surveillance against cells exhibiting pre-cancerous change [75,76].

In the setting of iALCL, breast implant-associated NHL are most commonly isolated in the fibrotic capsule and seroma fluid surrounding the implant [77]. The formation of these capsular tissues is in itself an inflammatory foreign body reaction resulting from the activation of macrophages, fibroblasts, and expansion of T lymphocytes (Fig. 2) [77–83]. Indeed, the expansion of inflammatory T-lymphocytes may be the source of iALCL whereby tumour cells express cell surface markers typically associated with an activated phenotype; tumour cells express the activation marker CD30 and produce cytotoxic molecules such as Perforin and Granzyme B [35]. Likewise, breast iALCL often express the same or similar surface markers indicative of a transformed and activated T-cell origin [22,47,54]. In further evidence, 3 cell lines have been developed to represent this disease and all 3 express CD30, produce Granzyme B and are of a T-cell phenotype as evidenced by the presence of clonal T-cell receptor rearrangements [84].

Interestingly, a recent review by Miranda et al. [29] suggested that there may be two subtypes of iALCL. First, iALCL of limited disease with no discrete tumour mass have been observed to achieve high rates of disease regression following treatment with capsulotomy, suggesting that this subset of iALCL may represent lymphoproliferations which are still very much dependent on the antigenic stimulus for survival and expansion and therefore may be amenable to a more conservative therapeutic approach of capsulotomy alone [29]. Indeed, the three aforementioned iALCL-derived cell lines are still dependent on IL2 for growth in vitro [84]. Whilst this does not equate to spontaneous involution of residual tumour cells left within patients after implant removal, it supports the clinical observation that iALCL with limited disease may be clonal but not autonomous.

However, in the remaining cases of iALCL, a higher proportion of patients continue to progress and even die from their disease despite surgery, suggesting that these cases of iACLC may have become independent of the antigenic stimulus and have perhaps acquired genetic mutations enabling autonomous survival. The identity of the driving genetic events remains to be determined but activating Notch mutations have been implicated [84].

Furthermore, chemotherapy was not shown in this review of 60 patients to improve overall progression-free survival at a mean

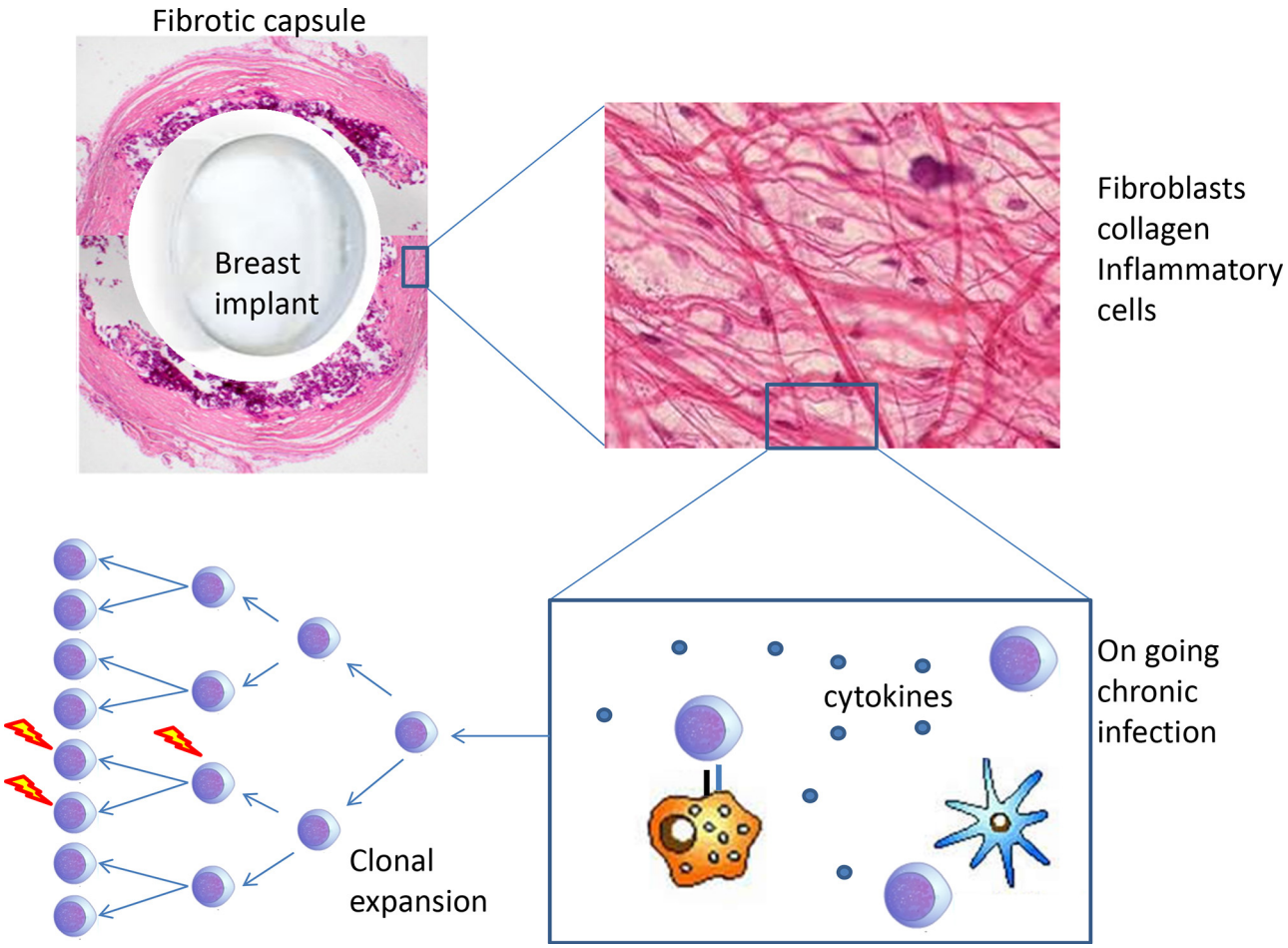

Fig. 2. Mechanisms of iALCL pathogenesis. A foreign body reaction in the host results in the formation of a fibrous capsule around the implant. This process begins at implantation as the implant is almost immediately covered, after its insertion, by a thin film of protein. Shortly after this, a fibrous matrix develops from the periprosthetic thrombus. This in turn triggers an inflammatory cascade through the intrinsic, extrinsic fibrinolytic, complement and kinin pathways, resulting in the activation of macrophages, lymphocytes and fibroblasts and ultimately culminating in a foreign body reaction against the implant material and the formation of a fibrous capsule. The chronic presence of a foreign body can result in the prolonged stimulation of lymphocytes, thereby causing delayed hypersensitivity reactions, aberrant wound healing and, over time, the expansion of T-cells. One might envisage a scenario whereby chronic inflammation leads to the expansion and continued proliferation of an activated T-cell pool which in time acquires mutations allowing cellular transformation and may become independent of the antigenic stimulus for growth.

follow-up of 2 years and no patients experienced spontaneous regression of disease without treatment, lending additional support to the notion that the biological stimulus of the implant and peri-capsular tissue may be the driving force underpinning the pathogenesis of iALCL [29]. However, we do stress that these results need to be interpreted with due caution given the limitations with analysing case report data.

3.2. Inflammatory oncotaxis and immunological escape

Inflammatory oncotaxis refers to the attraction to and activation of circulating neoplastic cells within a host by an inflamed tissue space. This concept was first described by Paget in 1889 who wrote "*When a plant goes to seed, its seeds are carried in all directions. . .but they can only live and grow if they fall on congenial soil.*" [85]. Since then, a number of authors have described instances of late tumour recurrence in inflamed tissues distant to the site of origin. Of particular interest are case reports of delayed metastasis to and development of lymphomas around fibrous pockets surrounding cardiovascular prostheses, a scenario that is remarkably similar to the seeding of ALCL tumour cells in the fibrous capsule and periprosthetic fluid around breast implants [61,86–88]. It has been suggested that fibrotic tissues provide the necessary stromal support and extracellular matrix for tumours to progress and thus providing the 'congenial soil' on which circulating and transformed cells can 'seed'.

The fibrous capsule surrounding breast implants may facilitate tumour escape from the immune system. The importance of the immune system in tumour suppression is well evidenced by both epidemiological and experimental models where immune-deficient hosts develop or can be induced into developing malignancies [89]. Interestingly, the majority of these malignancies are lymphomas [89].

'Immunosurveillance' is the detection and destruction of circulating precancerous cells which have escaped intrinsic tumour suppression mechanisms. When the clearance of tumour cells is incomplete, a state of temporary equilibrium arises between continued tumour evolution and immune elimination of tumour cells. This immunological 'arms race' between the tumour and the host is known as 'immunoediting' and tumours can thus remain dormant for years until the equilibrium is disturbed, resulting in tumour escape [76,89]. The provision of a permissive mesenchymal microenvironment has been hypothesized to be a critical step in providing tumours with a congenial environment from which to evade the immune system through:

(1) Creating immunological anergy via inappropriate co-stimulation of T lymphocytes, expression of inhibitory molecules, down-regulation of MHC molecules [89,90];
(2) Inhibition of immune-infiltration through down-regulation of adhesion molecules and the formation of physical barriers to antigen presentation [90];
(3) Stimulating the expression of immunosuppressive and anti-apoptotic factors produced by tumours [89].
(4) Inhibition of immune-infiltration through down-regulation of adhesion molecules and the formation of physical barriers to antigen presentation [90]; and
(5) Stimulating the expression of immunosuppressive and anti-apoptotic factors produced by tumours [89].

The fibrous capsule and periprosthetic fluid in which the majority of iALCL are found may provide such a friendly micro-environment, although it is not possible to determine based on available information, whether the potential mechanism is related to tumours in distant tissues colonizing the breast capsule via oncotaxis, or if clonal expansions of tumour cells arising at the site of the implant are encouraged to remain in the area. Both mechanisms are possible although most proponents of this theory believe that the former is more plausible.

3.3. Immunogenicity of implants

If iALCL is a distinct disease entity one would assume that device-related factors of the implant likely contribute to disease pathogenesis. Specifically, the composition and/or texture of a particular implant may be a 'trigger' and/or contribute to tumorigenesis.

3.3.1. Composition – silicone

The majority of the implant devices reported in the 71 cases examined contained silicone, either as a filling or as part of the outer shell. Medical grade silicone is one of the most biologically inert materials available and is used in a range of prosthetic devices including pacemakers, ventriculo-peritoneal shunts and prosthetic joints. However, over the last few decades, in light of reports of autoimmune disease, silicone adenopathy and cancer occurring in patients with silicone devices, there has been increasing concern amongst both medical professionals and the wider community as to the potential immunogenic and carcinogenic effects of silicone when implanted in the human body [77,79,91–96].

There are two leading schools of thought as to the potential mechanism through which silicone can exert toxicity. The first hypothesized mechanism is that silicone and silicone degradation products are directly toxic to living tissues. In evidence, the subcutaneous implantation of silicone gel has been shown to induce plasmacytomas in genetically predisposed mice [22,23,97]. The implication of this finding is potentially alarming given that silicone gels often 'bleed' through implant shells – indeed, silicone particles have been reported to be present in the axillary lymph nodes of over 90% of breast implant patients [77,94,98]; and once spread into tissue, leaked silicone gel can augment the production and release of interferon and TNF-α (in comparison to controls), which in turn can cause granulomatous and fibrotic reactions with cytological abnormalities that, over time, may lead to the clonal expansion of lymphocytes [94].

Even if the view is taken that silicone itself is inert, the prolonged presence of silicone in living tissue may nevertheless induce a foreign body response which can, over time, result in the degradation of that silicone into its toxic breakdown products, such as siloxane – which is an inducer of protein denaturation – and platinum and silicates – which are known cellular irritants and potential inducers of fibrosis [77,79,81,82,93]. Each of these three compounds have been detected in significant concentrations in the fibrous capsule surrounding silicone implants and represents a significant toxicological issue for patients with silicone prostheses [77]. Recently, cytometric studies by Wolfram et al. [99] on peri-capsular lymphocytes have confirmed the findings of earlier histological studies that silicone and silicone breakdown products induce, when combined with autologous proteins, an inflammatory response.

3.3.2. Implant texture

In addition to the chemical properties of silicone, the particular texture of an implant surface has also been suggested as a potential factor in the development of late seromas and iALCL [47,48,100].

Since the early 1960s, animal models have demonstrated that there are distinctive histological differences in the fibroblastic response to smooth implant surfaces and powdered implant surfaces [101]. Specifically, the subcutaneous implantation of smooth surfaces induces the formation of thick, densely packed and laminar connective tissue fibres which envelope the implant. The tissue reaction to smooth surfaces is associated with intense fibroblastic and giant cell activity which regresses upon implant removal. Cytologically, this more aggressive fibroblastic reaction can be explained by the observation that fibroblasts cultured from smooth implants are more effective in lowering the rate of transforming growth factor 1 (TGF-1) – a cytokine which regulates cellular proliferation – than their textured counterparts [102].

In contrast, the implantation of powdered surfaces – even into a pre-formed tissue pocket around a smooth surface – results in the formation of loose and irregularly-arranged collagen fibres with few active fibroblasts but numerous giant cells, possibly as a result of anoikis or apoptosis of the capsule lining due to its detachment from its supportive matrix [77,80]. Unlike smooth surfaces, powdered surfaces cannot easily be removed and thus the giant cell response can remain indefinitely (even after the removal of the smooth surface backing) and cause chronic irritation to the periprosthetic tissue [101].

Although the precise pathophysiological mechanism of double capsules and late seromas remain the subject of speculation, recent observations that these conditions occur almost exclusively in patients with textured implants lend support to the proposition that textured surfaces impede the adherence of cells to the implant surface, thereby resulting in tenuous 'Velcro-like' scar tissue which detaches with minor trauma [103]. The resulting 'shear' force between the two dissected surfaces in turn leads to cellular irritation, inflammation and seroma formation [103].

Based on the above observations, and the disproportionate occurrence of late seromas in ALCL patients compared to the general breast implant population (35.6% vs. 0.1%), the occurrence of late seromas is widely regarded by the plastic surgery community to be associated with the pathogenesis of ALCL although no causal relationship has yet been defined [103–105].

3.4. Subclinical infection as a carcinogen

Breast tissue is considered a 'clean-contaminated' surgical site as its ducts and glands communicate with the external environment. In a study where intra-operative swabs were taken from sterilized breast tissue, bacterial colonies were isolated in 38% of specimens [106]. Furthermore, scanning electron microscopy of swab-negative implants and capsules from women with capsular contractures have demonstrated that 38.5% of implants with Baker grade III/IV contractures are associated with a biofilm of coagulase negative bacteria compared to only 12.5% in patients with mild or no contractures [107]. Also, the deliberate inoculation of implants with staphylococcus in porcine models results in a 4.17-fold increase in the incidence of grade III/IV contractures compared to uncontaminated implants [108].

How does this relate to iALCL? A recent review has suggested that 16.1% of all new cancer diagnoses are attributable to infections [109]. Indeed, there is a substantial body of evidence linking prolonged infection with select pathogens to lymphoma formation including helicobacter pylori and mucosa-associated lymphoid tissue lymphoma, Epstein–Barr virus and Hodgkin lymphoma, and Human Herpes Virus-8 and primary effusion lymphoma [109–112].

However, a direct link between bacterial and/or viral contamination and ALCL of any form has not yet been demonstrated. Recently, 3 cell lines derived from iALCL were all determined to be negative for EBV, HTLV and HPV [84]. Therefore, although there is currently no definitive proof of an association between implant infection and lymphoma formation, the induction of ALCL by a yet to be defined pathogen is a distinct theoretical possibility which remains to be discounted. Applying the same train of thought, ALCL has been reported in the context of insect bites whereby it is assumed that antigens resulting from the bite drive infection, later leading to lymphoma development derived from the infiltrating T-cells – in these cases, ALCL is ALK^+ and hence this likely also contributes to disease pathogenesis [113]. The identity of these antigens remains elusive but could be related to infection at the site of the bite.

4. Therapeutic approaches

A number of treatments have been used in the reported cases including implant removal and capsulotomy, lymph node dissection, chemotherapy, radiotherapy and even autologous stem cell transplantation. However, given the small number of patients analyzed, heterogeneity of therapies employed and limited length of follow-up, it is difficult to determine the specific effect of each intervention for any achieved outcome.

The simplest approach is removal of the implant and its associated fibrotic capsule and there is evidence to suggest that this procedure alone is sufficient to remove disease particularly in those patients with lymphoma restricted to the fluid cavity bound by the capsule [29]. Various chemotherapeutic regimens have also been used although no significant improvement in overall progression-free survival has yet been demonstrated [29]. It would appear from the lack of clinical or empirical evidence guiding the use of chemotherapy of iALCL that most oncologists have opted to treat their patients based on existing NHL protocols. The most common regimen reported is CHOP (26/43 reported) and most patients enter remission or resolution of their disease (41/49 reported) at a mean of 15 months follow-up (range 1–52). A small proportion of treated individuals fail to respond to therapy and questions have been raised about a more aggressive phenotype for iALCL [3,5]. In particular, patients that present with a mass rather than a disease confined within the fibrous capsule have a lower rate of complete remission ($p = 0.18$)[29]. Similarly, the efficacy of radiation therapy is yet to be determined. This has led oncologists in search of novel therapeutic options.

Aside from ALK positivity/negativity, elevated CD30 expression is a defining feature of all forms of ALCL and hence the CD30 biomarker is a highly promising target for therapies aimed at modulating tumour cells [114]. Given that CD30 is generally not expressed on circulating lymphocytes, therapies that target this protein should have limited side effects and so several approaches have been studied to utilize and exploit CD30 expression. Targeting approaches have included radio-immunoconjugates, immunotoxins, immunoRNAses, immunokinases, and antibody drug conjugates (ADCs) [114]. Notably, in 2011 the ADC brentuximab-vedotin (SGN35) was approved for patients with refractory and relapsed Hodgkin lymphoma and ALCL. SGN 35 is composed of the CD30 specific chimeric monoclonal antibody cAC10 combined with the potent Tubulin toxin monomethyl auristatin E [115]. Given the efficacy of this drug initially in xenograft models and then in phases I and II clinical trials it is now being incorporated into the upfront management of CD30+ lymphoma [115]. It is likely that the use of CD30 targeting agents will further enhance survival as an adjunct to current first line chemotherapeutics for patients with all ALCL diagnostic entities including iALCL, where the predominant subtype does not harbour the ALK translocation amenable to tyrosine kinase inhibition. However, for those rare cases of iALCL that do aberrantly express ALK, kinase inhibitors might also be considered as a therapeutic approach. Many inhibitors of the ALK protein are now in preclinical and clinical development although the Pfizer compound Crizotinib has so far been the most extensively employed having been approved by the FDA in 2011. Crizotinib shows efficacy in the treatment of patients with NSCLC expressing the chromosomal inversion protein product, EML4/ALK. Indeed, Crizotinib also demonstrates efficacy in patients with ALCL, ALK^+ and some cases of neuroblastoma whereby the ALK gene is either amplified or expressed as a point mutation [116].

5. Conclusions

With an ever-growing database of ALCL cases occurring around breast implants worldwide, it is becoming more apparent that iALCL is very much a distinct clinical entity. We present a synopsis of the possible pathophysiological mechanisms for tumorigenesis based on the available basic science literature although there remain many unanswered questions surrounding this rare disease entity.

Conflict of interest

The authors declare that there is no source of financial or other support, or any financial or professional relationship which may pose a competing interest. KS undertook a breast reconstruction fellowship sponsored by Mentor, a subsidiary of Johnson and Johnson and major manufacturer of breast implants.

Acknowledgements

We are grateful to Dr Hongxiang Liu of the Molecular Diagnostics Service at Addenbrooke's Hospital, Cambridge, UK for the provision of images presented in Fig. 1. SDT is supported by a lectureship award funded by Leukaemia and Lymphoma Research(Grant number 12065). The sponsors had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication

References

[1] Administration UFaD, Anaplastic large cell lymphoma (ALCL) in women with breast implants: preliminary findings and analyses, 2011.
[2] Surgeons ASoP, Report of the 2010 Plastic Surgery Statistics, 2011.
[3] B. Alobeid, D.W. Sevilla, M.B. El-Tamer, V.V. Murty, D.G. Savage, G. Bhagat, Aggressive presentation of breast implant-associated ALK-1 negative anaplastic large cell lymphoma with bilateral axillary lymph node involvement, Leuk. Lymphoma 50 (5) (2009) 831–833.
[4] M.R. Bishara, C. Ross, M. Sur, Primary anaplastic large cell lymphoma of the breast arising in reconstruction mammoplasty capsule of saline filled breast implant after radical mastectomy for breast cancer: an unusual case presentation, Diagn. Pathol. 4 (2009) 11.
[5] M.J. Carty, J.J. Pribaz, J.H. Antin, et al., A patient death attributable to implant-related primary anaplastic large cell lymphoma of the breast, Plast. Reconstr. Surg. 128 (3) (2011) 112e–118e.
[6] D. de Jong, W.L. Vasmel, J.P. de Boer, et al., Anaplastic large-cell lymphoma in women with breast implants, JAMA 300 (17) (2008) 2030–2035.
[7] V. Do, D.A. Shifrin, L. Oostendorp, Lymphoma of the breast capsule in a silicone implant-reconstructed patient, Am. Surg. 76 (9) (2010) 1030–1031.

[8] E.A. Farkash, J.A. Ferry, N.L. Harris, et al., Rare lymphoid malignancies of the breast: a report of two cases illustrating potential diagnostic pitfalls, J. Hematopathol. 2 (4) (2009) 237–244.
[9] F.R. Fritzsche, S. Pahl, I. Petersen, et al., Anaplastic large-cell non-Hodgkin's lymphoma of the breast in periprosthetic localisation 32 years after treatment for primary breast cancer—a case report, Virch. Arch. 449 (5) (2006) 561–564.
[10] G. Gaudet, J.W. Friedberg, A. Weng, G.S. Pinkus, A.S. Freedman, Breast lymphoma associated with breast implants: two case-reports and a review of the literature, Leuk. Lymphoma 43 (1) (2002) 115–119.
[11] G. Gualco, L. Chioato, W.J. Harrington Jr., L.M. Weiss, C.E. Bacchi, Primary and secondary T-cell lymphomas of the breast: clinico-pathologic features of 11 cases, Appl. Immunohistochem. Mol. Morphol. 17 (4) (2009) 301–306.
[12] S.E. Hanson, K.A. Gutowski, Primary T-cell lymphoma associated with breast implant capsule, Plast. Reconstr. Surg. 126 (1) (2010) 39e–41e.
[13] J.A. Keech Jr., B.J. Creech, Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant, Plast. Reconstr. Surg. 100 (2) (1997) 554–555.
[14] D.M. Kraemer, H.P. Tony, S. Gattenlohner, J.G. Muller, Lymphoplasmacytic lymphoma in a patient with leaking silicone implant, Haematologica 89 (4) (2004) ELT01.
[15] D. Lazzeri, T. Agostini, G. Bocci, et al., ALK-1-negative anaplastic large cell lymphoma associated with breast implants: a new clinical entity, Clin. Breast Cancer 5 (2011) 283–296.
[16] S. Li, A.K. Lee, Silicone implant and primary breast ALK1-negative anaplastic large cell lymphoma, fact or fiction? Int. J. Clin. Exp. Pathol. 3 (1) (2009) 117–127.
[17] R.N. Miranda, L. Lin, S.S. Talwalkar, J.T. Manning, L.J. Medeiros, Anaplastic large cell lymphoma involving the breast: a clinicopathologic study of 6 cases and review of the literature, Arch. Pathol. Lab. Med. 133 (9) (2009) 1383–1390.
[18] P. Mora, A.C. Melo, G.L.S. Amorim, A.A. Schelgia, Primary T-cell anaplastic lymphoma associated to a breast implant: case report, Hematol. J. 94 (2009) 658–659.
[19] M.K. Newman, N.J. Zemmel, A.Z. Bandak, B.J. Kaplan, Primary breast lymphoma in a patient with silicone breast implants: a case report and review of the literature, J. Plast. Reconstr. Aesthetic Surg. 61 (7) (2008) 822–825.
[20] B. Olack, R. Gupta, G.S. Brooks, Anaplastic large cell lymphoma arising in a saline breast implant capsule after tissue expander breast reconstruction, Ann. Plast. Surg. 59 (1) (2007) 56–57.
[21] L. Popplewell, S.H. Thomas, Q. Huang, K.L. Chang, S.J. Forman, Primary anaplastic large-cell lymphoma associated with breast implants, Leuk. Lymphoma 52 (8) (2011) 1481–1487.
[22] A.C. Roden, W.R. Macon, G.L. Keeney, J.L. Myers, A.L. Feldman, A. Dogan, Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: an indolent T-cell lymphoproliferative disorder, Mod. Pathol. 21 (4) (2008) 455–463.
[23] P.A. Thompson, S. Lade, H. Webster, G. Ryan, H.M. Prince, Effusion-associated anaplastic large cell lymphoma of the breast: time for it to be defined as a distinct clinico-pathological entity, Haematologica 95 (11) (2010) 1977–1979.
[24] W. Cheuk, J.K. Chan, Timely topic: anaplastic lymphoma kinase (ALK) spreads its influence, Pathology 33 (1) (2001) 7–12.
[25] S. Sahoo, P.P. Rosen, R.M. Feddersen, D.S. Viswanatha, D.A. Clark, A. Chadburn, Anaplastic large cell lymphoma arising in a silicone breast implant capsule: a case report and review of the literature, Arch. Pathol. Lab. Med. 127 (3) (2003) e115–e118.
[26] T.J. Smith, R. Ramsaroop, Breast implant related anaplastic large cell lymphoma presenting as late onset peri-implant effusion, Breast 21 (1) (2012) 102–104.
[27] S.S. Talwalkar, R.N. Miranda, J.R. Valbuena, M.J. Routbort, A.W. Martin, L.J. Medeiros, Lymphomas involving the breast: a study of 106 cases comparing localized and disseminated neoplasms, Am. J. Surg. Pathol. 32 (9) (2008) 1299–1309.
[28] A.K. Wong, J. Lopategui, S. Clancy, D. Kulber, S. Bose, Anaplastic large cell lymphoma associated with a breast implant capsule: a case report and review of the literature, Am. J. Surg. Pathol. 32 (8) (2008) 1265–1268.
[29] R.N. Miranda, T.N. Aladily, H.M. Prince, et al., Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients, J. Clin. Oncol. 32 (2) (2014) 114–120.
[30] D. Benharroch, Z. Meguerian-Bedoyan, L. Lamant, et al., ALK-positive lymphoma: a single disease with a broad spectrum of morphology, Blood 91 (6) (1998) 2076–2084.
[31] B. Falini, S. Pileri, P.L. Zinzani, et al., ALK$^+$ lymphoma: clinico-pathological findings and outcome, Blood 93 (8) (1999) 2697–2706.
[32] L. Brugieres, M.C. Deley, H. Pacquement, et al., CD30(+) anaplastic large-cell lymphoma in children: analysis of 82 patients enrolled in two consecutive studies of the French Society of Pediatric Oncology, Blood 92 (10) (1998) 3591–3598.
[33] H. Stein, H.D. Foss, H. Durkop, et al., CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features, Blood 96 (12) (2000) 3681–3695.
[34] R. Willemze, E.S. Jaffe, G. Burg, et al., WHO-EORTC classification for cutaneous lymphomas, Blood 105 (10) (2005) 3768–3785.
[35] S.H. Swerdlow, WHO classification of tumours of haematopoietic and lymphoid tissues, International Agency for Research on Cancer, Lyon, 2008, 439pp..
[36] K.J. Savage, N.L. Harris, J.M. Vose, et al., ALK-anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project, Blood 111 (12) (2008) 5496–5504.
[37] S.D. Turner, D.R. Alexander, Fusion tyrosine kinase mediated signalling pathways in the transformation of haematopoietic cells, Leukemia 20 (4) (2006) 572–582.
[38] R. Chiarle, W.J. Simmons, H. Cai, et al., Stat3 is required for ALK-mediated lymphomagenesis and provides a possible therapeutic target, Nat. Med. 11 (6) (2005) 623–629.
[39] Q. Zhang, P.N. Raghunath, L. Xue, et al., Multilevel dysregulation of STAT3 activation in anaplastic lymphoma kinase-positive T/null-cell lymphoma, J. Immunol. 168 (1) (2002) 466–474.
[40] O. Merkel, F. Hamacher, E. Sifft, L. Kenner, R. Greil, European Research Initiative on Anaplastic Large Cell L. Novel therapeutic options in anaplastic large cell lymphoma: molecular targets and immunological tools, Mol. Cancer Ther. 10 (7) (2011) 1127–1136.
[41] A.L. Feldman, A. Dogan, D.I. Smith, et al., Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing, Blood 117 (3) (2011) 915–919.
[42] M. Boi, A. Rinaldi, I. Kwee, et al., PRDM1/BLIMP1 is commonly inactivated in anaplastic large T-cell lymphoma, Blood 122 (15) (2013) 2683–2693.
[43] L. Agnelli, E. Mereu, E. Pellegrino, et al., Identification of a 3-gene model as a powerful diagnostic tool for the recognition of ALK-negative anaplastic large-cell lymphoma, Blood 120 (6) (2012) 1274–1281.
[44] O. Merkel, F. Hamacher, D. Laimer, et al., Identification of differential and functionally active miRNAs in both anaplastic lymphoma kinase (ALK)$^+$ and ALK$^-$ anaplastic large-cell lymphoma, Proc. Natl. Acad. Sci. U. S. A. 107 (37) (2010) 16228–16233.
[45] H.L. Liu, R.T. Hoppe, S. Kohler, J.D. Harvell, S. Reddy, Y.H. Kim, CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma, J. Am. Acad. Dermatol. 49 (6) (2003) 1049–1058.
[46] M.W. Bekkenk, F.A. Geelen, P.C. van Voorst Vader, et al., Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment, Blood 95 (12) (2000) 3653–3661.
[47] B. Kim, C. Roth, K.C. Chung, et al., Anaplastic large cell lymphoma and breast implants: a systematic review, Plast. Reconstr. Surg. 127 (6) (2011) 2141–2150.
[48] B. Kim, C. Roth, V.L. Young, et al., Anaplastic large cell lymphoma and breast implants: results from a structured expert consultation process, Plast. Reconstr. Surg. 128 (3) (2011) 629–639.
[49] M. Jewell, S.L. Spear, J. Largent, M.G. Oefelein, W.P. Adams Jr., Anaplastic large T-cell lymphoma and breast implants: a review of the literature, Plast. Reconstr. Surg. 128 (3) (2011) 651–661.
[50] B. Bengtson, G.S. Brody, M.H. Brown, et al., Managing late periprosthetic fluid collections (seroma) in patients with breast implants: a consensus panel recommendation and review of the literature, Plast. Reconstr. Surg. 128 (1) (2011) 1–7.
[51] K.C. Chung, Discussion managing late periprosthetic fluid collections (seroma) in patients with breast implants: a consensus panel recommendation and review of the literature, Plastic Reconstr. Surg. 128 (1) (2011) 13–16.
[52] P.C. Haeck, F.F. Eaves 3rd., Discussion: diagnosis and management of seroma following breast augmentation: an update, Plastic Reconstr. Surg. 128 (1) (2011) 29–31.
[53] M.G. Lechner, S. Lade, D.J. Liebertz, et al., Breast implant-associated, ALK-negative, T-cell, anaplastic, large-cell lymphoma: establishment and characterization of a model cell line (TLBR-1) for this newly emerging clinical entity, Cancer 117 (7) (2011) 1478–1489.
[54] M.E. Kadin, C. Carpenter, Systemic and primary cutaneous anaplastic large cell lymphomas, Semin. Hematol. 40 (3) (2003) 244–256.
[55] B.C. Kellogg, M.E. Hiro, W.G. Payne, Implant-associated anaplastic large cell lymphoma: beyond breast prostheses, Ann. Plast. Surg. (2013), http://dx.doi.org/10.1097/SAP.0b013e31827faff2.
[56] W. Cheuk, A.C. Chan, J.K. Chan, G.T. Lau, V.N. Chan, H.H. Yiu, Metallic implant-associated lymphoma: a distinct subgroup of large B-cell lymphoma related to pyothorax-associated lymphoma? Am. J. Surg. Pathol. 29 (6) (2005) 832–836.
[57] N.M. Durrleman, I. El-Hamamsy, R.G. Demaria, M. Carrier, L.P. Perrault, B. Albat, Cardiac lymphoma following mitral valve replacement, Ann. Thoracic Surg. 79 (3) (2005) 1040–1042.
[58] P. Paavolainen, E. Pukkala, P. Pulkkinen, T. Visuri, Cancer incidence in Finnish hip replacement patients from 1980 to 1995: a nationwide cohort study involving 31,651 patients, J. Arthroplasty 14 (3) (1999) 272–280.
[59] B. Palraj, A. Paturi, R.G. Stone, et al., Soft tissue anaplastic large T-cell lymphoma associated with a metallic orthopedic implant: case report and review of the current literature, J. Foot Ankle Surg. Off. Publ. Am. College Foot Ankle Surg. 49 (6) (2010) 561–564.
[60] T. Visuri, P. Pulkkinen, P. Paavolainen, Malignant tumors at the site of total hip prosthesis. Analytic review of 46 cases, J. Arthroplasty 21 (3) (2006) 311–323.
[61] N. Hojo, Y. Yakushijin, H. Narumi, et al., Non-Hodgkin's lymphoma developing in a pacemaker pocket, Int. J. Hematol. 77 (4) (2003) 387–390.
[62] T. Onega, J. Baron, T. MacKenzie, Cancer after total joint arthroplasty: a meta-analysis, Cancer Epidemiol. Biomark. Prev. 15 (8) (2006) 1532–1537.
[63] L.A. Brinton, J.H. Lubin, M.C. Burich, T. Colton, S.L. Brown, R.N. Hoover, Cancer risk at sites other than the breast following augmentation mammoplasty, Ann. Epidemiol. 11 (4) (2001) 248–256.
[64] D.M. Deapen, E.M. Hirsch, G.S. Brody, Cancer risk among Los Angeles women with cosmetic breast implants, Plast. Reconstr. Surg. 119 (7) (2007) 1987–1992.
[65] S. Friis, L.R. Holmich, J.K. McLaughlin, et al., Cancer risk among Danish women with cosmetic breast implants, Int. J. Cancer 118 (4) (2006) 998–1003.
[66] L. Lipworth, R.E. Tarone, S. Friis, et al., Cancer among Scandinavian women with cosmetic breast implants: a pooled long-term follow-up study, Int. J. Cancer 124 (2) (2009) 490–493.

[67] L. Lipworth, R.E. Tarone, J.K. McLaughlin, Breast implants and lymphoma risk: a review of the epidemiologic evidence through 2008, Plast. Reconstr. Surg. 123 (3) (2009) 790–793.
[68] E. Pukkala, J.D. Boice Jr., S.L. Hovi, et al., Incidence of breast and other cancers among Finnish women with cosmetic breast implants, 1970–1999, J. Long. Term Eff. Med. Implant. 12 (4) (2002) 271–279.
[69] D.L. McCauley, High-dose chemotherapy with stem-cell rescue for the treatment of breast cancer, Am. J. Health. Syst. Pharm. 53 (5) (1996) 521–534, quiz 561-522.
[70] J.K. McLaughlin, L. Lipworth, D.K. Murphy, P.S. Walker, The safety of silicone gel-filled breast implants: a review of the epidemiologic evidence, Ann. Plast. Surg. 59 (5) (2007) 569–580.
[71] P. Wagner, H. Olsson, L. Lidgren, O. Robertsson, J. Ranstam, Increased cancer risks among arthroplasty patients: 30 year follow-up of the Swedish Knee Arthroplasty Register, Eur. J. Cancer 47 (7) (2011) 1061–1071.
[72] J.P. Fryzek, W. Ye, L.B. Signorello, et al., Incidence of cancer among patients with knee implants in Sweden, 1980–1994, Cancer 94 (11) (2002) 3057–3062.
[73] T. Visuri, E. Pukkala, P. Paavolainen, P. Pulkkinen, E.B. Riska, Cancer risk after metal on metal and polyethylene on metal total hip arthroplasty, Clin. Orthop. (329 Suppl.) (1996) S280–S289.
[74] M.J. Goldacre, C.J. Wotton, V. Seagroatt, D. Yeates, Cancer following hip and knee arthroplasty: record linkage study, Br. J. Cancer 92 (7) (2005) 1298–1301.
[75] F. Colotta, P. Allavena, A. Sica, C. Garlanda, A. Mantovani, Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability, Carcinogenesis 30 (7) (2009) 1073–1081.
[76] D.F. Quail, J.A. Joyce, Microenvironmental regulation of tumor progression and metastasis, Nat. Med. 19 (11) (2013) 1423–1437.
[77] S.H. Yoshida, S. Swan, S.S. Teuber, M.E. Gershwin, Silicone breast implants: immunotoxic and epidemiologic issues, Life Sci. 56 (16) (1995) 1299–1310.
[78] R.M. Brohim, P.A. Foresman, P.K. Hildebrandt, G.T. Rodeheaver, Early tissue reaction to textured breast implant surfaces, Ann. Plast. Surg. 28 (4) (1992) 354–362.
[79] H. Busch, Silicone toxicology, Semin. Arthritis Rheum. 24 (1 Suppl. 1) (1994) 11–17.
[80] J.M. Anderson, A. Rodriguez, D.T. Chang, Foreign body reaction to biomaterials, Semin. Immunol. 20 (2) (2008) 86–100.
[81] A. Backovic, D. Wolfram, Silicone mammary implants—can we turn back the time? Exp. Gerontol. 42 (8) (2007) 713–718.
[82] D.R. Shanklin, D.L. Smalley, The immunopathology of siliconosis. History, clinical presentation, and relation to silicosis and the chemistry of silicon and silicone, Immunol. Res. 18 (3) (1998) 125–173.
[83] D.R. Shanklin, D.L. Smalley, Dynamics of wound healing after silicone device implantation, Exp. Mol. Pathol. 67 (1) (1999) 26–39.
[84] M.G. Lechner, C. Megiel, C.H. Church, et al., Survival signals and targets for therapy in breast implant-associated ALK$^-$ anaplastic large cell lymphoma, Clin. Cancer Res. 18 (17) (2012) 4549–4559.
[85] S. Paget, The distribution of secondary growths in cancer of the breast, 1889, Cancer Metastasis Rev. 8 (2) (1989) 98–101.
[86] D. Moruzzo, M. Bindi, M.G. Bongiorni, M. Castiglioni, A rare case of non-Hodgkin lymphoma in a pacemaker pocket, Leuk. Lymphoma 50 (8) (2009) 1384–1385.
[87] G. Fraedrich, J. Kracht, H.H. Scheld, G. Jundt, J. Mulch, Sarcoma of the lung in a pacemaker pocket—simple coincidence or oncotaxis? Thorac. Cardiovasc. Surg. 32 (1) (1984) 67–69.
[88] W.R. Hamaker, M.E. Lindell, A.C. Gomez, Plasmacytoma arising in a pacemaker pocket, Ann. Thoracic Surg. 21 (4) (1976) 354–356.
[89] J.B. Swann, M.J. Smyth, Immune surveillance of tumors, J. Clin. Invest. 117 (5) (2007) 1137–1146.
[90] F.H. Igney, P.H. Krammer, Immune escape of tumors: apoptosis resistance and tumor counterattack, J. Leukoc. Biol. 71 (6) (2002) 907–920.
[91] E. Benjamin, A. Ahmed, A.T. Rashid, D.H. Wright, Silicone lymphadenopathy: a report of two cases, one with concomitant malignant lymphoma, Diagn. Histopathol. 5 (2) (1982) 133–141.
[92] N. Brautbar, The silicone breast implant controversy. Silicone toxicity and autoimmunity, Natl. Med. Leg. J. 6 (2) (1995) 1, 4–7.
[93] M. Copeland, M. Choi, I.J. Bleiweiss, Silicone breakdown and capsular synovial metaplasia in textured-wall saline breast prostheses, Plastic Reconstr. Surg. 94 (5) (1994) 628–633, discussion 634-626..
[94] W.E. Katzin, J.A. Centeno, L.J. Feng, M. Kiley, F.G. Mullick, Pathology of lymph nodes from patients with breast implants: a histologic and spectroscopic evaluation, Am. J. Surg. Pathol. 29 (4) (2005) 506–511.
[95] L.A. Murakata, A.F. Rangwala, Silicone lymphadenopathy with concomitant malignant lymphoma, J. Rheumatol. 16 (11) (1989) 1480–1483.
[96] K. Rodgers, P. Klykken, J. Jacobs, C. Frondoza, V. Tomazic, J. Zelikoff, Immunotoxicity of medical devices. Symposium overview, Fundam. Appl. Toxicol.: Off. J. Soc. Toxicol. 36 (1) (1997) 1–14.
[97] M. Potter, S. Morrison, F. Wiener, X.K. Zhang, F.W. Miller, Induction of plasmacytomas with silicone gel in genetically susceptible strains of mice, J. Natl. Cancer Inst. 86 (14) (1994) 1058–1065.
[98] D.E. Barker, M.I. Retsky, S. Schultz, Bleeding of silicone from bag-gel breast implants, and its clinical relation to fibrous capsule reaction, Plast. Reconstr. Surg. 61 (6) (1978) 836–841.
[99] D. Wolfram, E. Rabensteiner, C. Grundtman, et al., T regulatory cells and TH17 cells in peri-silicone implant capsular fibrosis, Plast. Reconstr. Surg. 129 (2) (2012) 327e–337e.
[100] M.Y. Nahabedian, Discussion anaplastic large cell lymphoma and breast implants: results from a structured expert consultation process, Plast. Reconstr. Surg. 128 (3) (2011) 640–642.
[101] E.T. Oppenheimer, M. Willhite, I. Danishefsky, A.P. Stout, Observations on the effects of powdered polymer in the carcinogenic process, Cancer Res. 21 (1961) 132–134.
[102] H. Seyhan, J. Kopp, J.P. Beier, et al., Smooth and textured silicone surfaces of modified gel mammary prostheses cause a different impact on fibroproliferative properties of dermal fibroblasts, J. Plastic Reconstr. Aesthetic Surg. 64 (3) (2011) e60–e66.
[103] E.J. Hall-Findlay, Breast implant complication review: double capsules and late seromas, Plast. Reconstr. Surg. 127 (1) (2011) 56–66.
[104] M. Mazzocchi, L.A. Dessy, B. Carlesimo, F. Marchetti, N. Scuderi, Late seroma formation after breast surgery with textured silicone implants: a problem worth bearing in mind, Plast. Reconstr. Surg. 125 (4) (2010) 176e–177e.
[105] J.B. Tebbetts, Diagnosis and management of seroma following breast augmentation: an update, Plast. Reconstr. Surg. 128 (1) (2011) 17–25.
[106] S. Bartsich, J.A. Ascherman, S. Whittier, C.A. Yao, C. Rohde, The breast: a clean-contaminated surgical site, Aesthetic Surg. J. Am. Soc. Aesthetic Plastic Surg. 31 (7) (2011) 802–806.
[107] A. Pajkos, A.K. Deva, K. Vickery, C. Cope, L. Chang, Y.E. Cossart, Detection of subclinical infection in significant breast implant capsules, Plast. Reconstr. Surg. 111 (5) (2003) 1605–1611.
[108] H. Tamboto, K. Vickery, A.K. Deva, Subclinical (biofilm) infection causes capsular contracture in a porcine model following augmentation mammaplasty, Plastic Reconstr. Surg. 126 (3) (2010) 835–842.
[109] C. de Martel, J. Ferlay, S. Franceschi, et al., Global burden of cancers attributable to infections in 2008: a review and synthetic analysis, Lancet Oncol. 13 (6) (2012) 607–615.
[110] F. Bertoni, B. Coiffier, G. Salles, et al., MALT lymphomas: pathogenesis can drive treatment, Oncology (Williston Park) 25 (12) (2011) 1134–1142, 1147.
[111] E. Maeda, M. Akahane, S. Kiryu, et al., Spectrum of Epstein–Barr virus-related diseases: a pictorial review, Jpn. J. Radiol. 27 (1) (2009) 4–19.
[112] M.F. Li, C.H. Hsiao, Y.L. Chen, et al., Human herpesvirus 8-associated lymphoma mimicking cutaneous anaplastic large T-cell lymphoma in a patient with human immunodeficiency virus infection, J. Cutan. Pathol. 39 (2) (2012) 274–278.
[113] L. Lamant, S. Pileri, E. Sabattini, L. Brugieres, E.S. Jaffe, G. Delsol, Cutaneous presentation of ALK-positive anaplastic large cell lymphoma following insect bites: evidence for an association in five cases, Haematologica 95 (3) (2010) 449–455.
[114] T. Schirrmann, M. Steinwand, X. Wezler, A. Ten Haaf, M.K. Tur, S. Barth, CD30 as a therapeutic target for lymphoma, BioDrugs: Clin. Immunotherapeut. Biopharmaceut. Gene Therapy 28 (2) (2014) 181–209.
[115] C. Deng, B. Pan, O.A. O'Connor, Brentuximab vedotin, Clin. Cancer Res. 19 (1) (2013) 22–27.
[116] C. Murga-Zamalloa, M.S. Lim, ALK-driven tumors and targeted therapy: focus on crizotinib, Pharmacogenom. Personal. Med. 7 (2014) 87–94.